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PATENT
UMD 1-037CIP

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Patent Application Of:
Kirin K. Chada et al.

Group Art Unit: 1653

Serial No.: 08/852,666

Examiner: Devesh Srivastava

Filed: 7 May 1997

For: **HMGI PROTEINS IN CANCER AND OBESITY**

Honorable Commissioner of Patents and Trademarks
Washington; D.C. 20231

RESPONSE PURSUANT TO 37 C.F.R. SECTION 1.111

Sir:

This Response pursuant to 37 C.F.R. Section 1.111 is in reply to the Examiner's Action dated 28 October 1999 in the above-identified patent application in which claims 1-40 are pending, claims 1-5, 13-15, 20-22, 26-28, and 33-40 have been withdrawn subject to a restriction requirement, and claims 6-12, 16-19, 23-25 and 29-32 were rejected. A Response to this Action was originally due 28 January 2000. Applicants have petitioned, pursuant to 37 C.F.R. Section 1.136(a), concurrently herewith for a two (2) month extension to extend the time for response to the Examiner's Action dated 28 October 1999 for two months from

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CERTIFICATE OF MAILING PURSUANT TO 37 C.F.R. SECTION 1.8

I hereby certify that this correspondence and any documents referred to as enclosed herewith are being deposited, pursuant to 37 C.F.R. Section 1.8, with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231 on this 28th of March, 2000.

By Richard R. Muccino
Richard R. Muccino
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Attorney for Applicant(s)

date

28 January 2000 up to and including 28 March 2000 and have paid the required fee pursuant to 37 C.F.R. Sections 1.136(a) and 1.17. Applicants have also filed concurrently herewith a request for a patent application filing pursuant to the continuing prosecution application procedure in accord with 37 C.F.R. Section 1.53(d). Accordingly, this Response is timely filed.

Applicant requests that the Examiner consider the following Response, withdraw the pending rejections, and pass the above-identified application to issue.

RESPONSE

Claims 1-40 of the subject application are pending, claims 1-5, 13-15, 20-22, 26-28, and 33-40 have been withdrawn subject to a restriction requirement, claims 16 and 29 have been cancelled, and claims 6-12, 16-19, 23-25 and 29-32 were rejected. Accordingly, claims 6-12, 17-19, 23-25 and 30-32 are presently being examined.

In view of the following Response, applicants respectfully request that the Examiner reconsider and withdraw the rejections made in the outstanding Office Action.

Rejections of Claims 6-12, 17-19, 23-25 and 30-32 under 35 U.S.C. §112, first paragraph.

The Examiner has maintained the rejection of claims 6-12, 17-19, 23-25 and 30-32 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled

in the art to which it pertains, or with which it is most nearly connected, to use the invention. Specifically, the Examiner states that the specification discloses "The reduction in biological activity of HMGI genes may be achieved by inhibiting the DNA-binding activity of HMGI genes which may be carried out by administering to the mammal a therapeutically effective amount of netropsin, distamycin A or Hoechst 33258 (bisbenzimide)" but that the specification fails to disclose the composition in which any of the three drugs will be administered, the frequency of administration, the need for coincidental changes in behavior including diet and exercise or the effect of confounding factors such as diabetes. The Examiner asserts that since these drugs are not known in the art to reduce the *in vivo* activity of HMGI proteins, it cannot be predicted if such a reduction would occur. The Examiner notes that the specification discloses "The reduction in biological activity of HMGI genes may be achieved by inhibiting the expression of HMGI genes which may be carried out by administering to the mammal a therapeutically effective amount of an oligonucleotide which has a nucleotide sequence complementary to at least a portion of the mRNA of the HMGI gene" but that the specification has only general statements concerning the frequency, dosage, mode and site(s) of administration of antisense oligonucleotides and leaves these factors to be determined in accordance with conventional practice among medical or veterinary professionals. The Examiner points out that claim 16 recites inhibiting protein-protein interactions of HMGI proteins but that it is known that HMGI proteins regulate gene expression by functioning as architectural factors to induce conformational changes in DNA, however, the specification fails to disclose how the inhibition of protein-protein interactions of HMGI proteins would be accomplished as well as what compounds would be used to accomplish this goal. The Examiner concludes that given the unpredictability in the art, there is also a

lack of a working example in the specification, specifically, there is no example of a reduction in biological activity of an HMGI protein in a mammal that is produced by either of the disclosed methods quoted above, and hence in view of the unpredictability in the arts of treating obesity and antisense oligonucleotide technology, the lack of clear guidance with respect to dosage and frequency of administration of drugs or antisense oligonucleotides and the lack of a working example, one skilled in the art could not use the inventions of claims 6-12 and 16-19 without undue experimentation.

The Examiner further argues that applicants' arguments have been directed to situations encompassing growth and development of adipose tissue, which according to the arguments, also encompass abnormal (cancer or tumor) growth but that none of the arguments are directed to an actual method for regulating such processes, which is what was claimed in claims 23-25 and 30-32, and further, no arguments have been directed to claimed methods of treating obesity (claims 6-12 and 17-19). The Examiner maintains that while it may be true that some human lipomas have been linked to rearrangement at chromosome 12m bands q14-15 where HMGI-C is mapped, that this would "suggest a role for HMGI-C in adipogenesis" and that HMGI expression is activated in human lipomas, applicants have failed to demonstrate how this relates to the claimed invention of methods of regulating growth and development of adipose tissue. The Examiner maintains it is unclear how naturally occurring genetic defects in humans correspond to the claimed invention, which is directed to methods of treating obesity (claims 6-12 and 17-19) or to methods of regulating growth and development of adipose tissue (claims 23-25 and 30-32) in a mammal. The Examiner asserts that the murine knockout studies are also not directed to the claimed invention especially when considering that a mouse does not encompass the entire genus of mammal which

according to the specification may be human or rodent and that a decrease in stature by homologous recombination does not equate to a treatment of obesity or regulation of growth and development of adipose tissue. Further, the Examiner states that homologous recombination is not a method by which treatment of obesity or regulation of growth and development of adipose tissue is to be accomplished, as disclosed in the specification.

With respect to claims 6-12 and 16-19, the Examiner maintains that *Marx* states that "Few medical problems have proved to be more intractable than obesity" (page 1477, column 1, lines 1-2) and *Rink* states "...much remains to be done" towards therapeutic approaches to obesity (page 407, column 2, line 12). With respect to antisense oligonucleotide approaches to reduce biological activity of HMGI genes, the Examiner notes that *Branch* states "the antisense field has been turned on its head by the discovery of `non-antisense' effects, which occur when a nucleic acid drug acts on some molecule other than its intended target" and this "unpredictability confounds research applications of nucleic acid reagents." (page 45, column 2, lines 3-7 and 13-15), and that *Branch* further states "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules." (page 45, column 3, lines 1-5). The Examiner contends that the latter point illustrates the need for antisense oligonucleotides that are complementary to exposed regions of target RNA, and it is unclear if the disclosed antisense oligonucleotides are complementary to exposed regions of target RNA. The Examiner concludes that the art, as referenced above, suggest that there is much more to be done before effective treatments for obesity can be performed, and further, given the unpredictability in the art, there is also a lack of a working example in the specification, specifically, there is no example of a reduction in

biological activity of an HMGI protein in a mammal that is produced by either of the disclosed methods quoted above. The Examiner takes the position that in view of the unpredictability in the arts of treating obesity and antisense oligonucleotide technology, the lack of clear guidance with respect to dosage and frequency of administration of drugs or antisense oligonucleotides and the lack of a working example, one skilled in the art could not use the inventions of claims 6-12 and 16-19 without undue experimentation.

The Examiner notes that claims 23-25 and 29-32 recite methods for regulating growth and development of adipose tissue in a mammal, and according to the specification, the mammal may be human or rodent (page 11, lines 18-19, see discussion above for disclosed methods by which this would be accomplished as well as the discussion of why the art of antisense technology is unpredictable.) With respect to claims 23-25 and 29-32, the Examiner contends that HMGI proteins are suggested to play a role in adipogenesis (*Guerre-Millo et al.* and *Auwerx et al.*), however, *Guerre-Millo et al.* state "Although major progress has been made into clarifying the basic role of transcription factors in adipocyte differentiation, major challenges lie ahead before this can be extrapolated to the human situation." (page 1530, column 1, lines 20-23) and *Auwerx et al.* state "...studies should be designed to test whether results obtained using animal models and *in vitro* cell culture systems can be extrapolated to the human situation and eventually applied in medical practice. Although enormous progress has been made regarding the role which transcription factors play in adipocyte differentiation, major challenges lie ahead." (page 350, column 2, lines 1-7). The Examiner takes the position that the art, as referenced above, suggest that there is much more to be done before effective regulation of growth and development of adipose tissue (adipogenesis) can be performed, further, given the unpredictability in the art, there is also a lack of a

working example in the specification. Specifically, the Examiner argues that there is no example of a reduction in biological activity of an HMGI protein in a mammal that is produced by either of the disclosed methods. The Examiner concludes that in view of the unpredictability in the arts of regulating adipogenesis and antisense oligonucleotide technology, the lack of clear guidance with respect to dosage and frequency of administration of drugs or antisense oligonucleotides and the lack of a working example, one skilled in the art could not use the inventions of claims 23-25 and 29-32 without undue experimentation.

The Examiner concludes that methods of treating obesity and methods of regulating growth and development of adipose tissue are not well known in the art, although applicants assume that the necessary teachings exist in the art, and in fact, the Examiner has established that approaches to treating obesity or regulating growth and development of adipose tissue, even now, are not enabled in the art. The Examiner maintains that applicants have clearly failed to demonstrate that their methods are enabled, especially when the art teaches otherwise, and therefore, applicants have failed to teach how to use their claimed invention. Applicants traverse the Examiner's rejections.

Aberrations in the genetic mechanisms that control growth and proliferation have emerged as a primary event in carcinogenesis. The function of HMGI-C and HMGI(Y), two embryonically expressed DNA-binding proteins, was investigated because their expression is highly associated with tumor development. Disruptions of either HMGI-C or HMGI(Y) in humans result in a diverse array of solid mesenchymal tumors. Most prominent among these neoplasms are uterine leiomyomata, the most common pelvic tumors in women and the indication for over 200,000 hysterectomies annually in the United States. In tumors of mammary and thyroid glands as well as in prostate cancer, HMGI expression is highly correlated

with tumor progression and metastasis, suggesting that these proteins can be used for as progression markers for a variety of tumor types.

Further proof for the pivotal role of HMGI proteins in both normal and pathological growth was obtained in the mouse system. Homologous recombination was used to inactivate murine HMGI-C gene. Demonstrating the importance of the HMGI genes in growth regulation, HMGI-C knockout mice exhibit significant growth retardation (mutant mice are 60% smaller than their wild-type littermates) with the reduction in most tissues commensurate with the overall decrease in the body weight. Even more importantly, these pygmy mice are highly resistant to chemically induced skin cancer. Specifically, the frequency of tumor development in the knockout mice is 40% of that in the control animals and tumor multiplicity exhibits a 20-fold decrease. Independently, inhibition of HMGI-C synthesis was shown to render thyroid epithelial cells intransigent to retroviral transformation. At the molecular level, HMGI proteins function in transcriptional regulation by promoting cooperative binding of the transcription factors to DNA. Deregulation of the downstream target genes can easily account for the important biological roles of the HMGI proteins as well as for the dramatic consequences of their inappropriate expression.

Lipomas are one of the most common mesenchymal neoplasms in humans. They are characterized by consistent cytogenetic aberrations involving chromosome 12 in bands q14-15. Interestingly, this region is also the site of rearrangement for other mesenchymally derived tumors. The present invention demonstrates that HMGI-C, an architectural factor that functions in transcriptional regulation, has been disrupted by rearrangement at the 12q14-15 chromosomal breakpoint in lipomas. Chimeric transcripts were isolated from two lipomas in which HMGI-C DNA-binding domains (A-T hook motifs) are fused to either a LIM

or an acidic transactivation domain. These results identify the first gene rearranged in a benign neoplastic process that does not proceed to a malignancy and suggest a role for HMGI-C in adipogenesis and mesenchyme differentiation.

HMGI-C is an attractive candidate gene to be implicated in lipoma formation. This gene is required in transformation (Berlingieri et al., 1995) and is a transcriptional regulatory factor as are many genes identified at translocation breakpoints in a variety of tumors (Rabbitts, 1994). Secondly, disruption of HMGI-C leads to mice of small stature which, most intriguingly, have disproportionately less body fat than normal littermates (Benson and Chada, 1994). Finally, mouse HMGI-C maps to a region syntenic to human 12q14-15 which is the area most frequently rearranged in lipomas (Mandahl et al., 1988). Therefore, the human homolog of the mouse HMGI-C gene was cloned and its possible role in lipomas investigated.

Growth is one of the fundamental aspects in the development of an organism. Classical genetic studies have isolated four viable, spontaneous mouse mutants (Green, 1989) disrupted in growth, leading to dwarfism. Pygmy is unique among these mutants because its phenotype cannot be explained by aberrations in the growth hormone-insulin-like growth factor endocrine pathway (Lin, 1993; Li, et al., 1990; Sinha et al., 1979; Nissley et al., 1980). The present invention shows that the pygmy phenotype arises from the inactivation of HMGI-C and are critical in the assembly of stereospecific transcriptional complexes (Tjian & Maniatis, 1994). In addition, HMGI-C and the other HMGI family member, HMGI(Y)(Johnson et al., 1988), were found to be expressed predominantly during embryogenesis. The HMGI family are known to be regulated by cell cycle dependent phosphorylation which alters their DNA binding affinity (Reeves et al.,

1991). Overall, these results demonstrate the important role of HMGI proteins in mammalian growth and development.

Among the most prominent characteristics consistently exhibited by cancer cells are karyotypic aberrations which disturb genes essential for the regulation of fundamental cellular processes. A wide array of solid mesenchymal tumors is characterized by recurrent rearrangements of chromosomal bands 12q13-15 or 6p21-23. This study shows that HMGI expression is normally restricted to undifferentiated, rapidly dividing cells but is activated in differentiated adipocytes following translocations of 12q13-15 or 6p21-23 in human lipomas. The present invention shows that the molecular pathway of tumor development is dictated by the precise nature of HMGI disruption and that HMGI misexpression in a differentiated cell is a pivotal event in benign tumorigenesis.

Uterine leiomyomata are the most common pelvic tumors in women and are the indication for more than 200,000 hysterectomies annually in the United States. Rearrangement of chromosome 12 in bands q14-q15 is characteristic of uterine leiomyomata and other benign mesenchymal tumors, and a YAC spanning chromosome 12 translocation breakpoints was identified in a uterine leiomyoma, pulmonary chondroid hamartoma, and lipoma. Recently, it was demonstrated that HMGI-C, an architectural factor mapping within the YAC, is disrupted in lipomas, resulting in novel fusion transcripts. This study concerns the localization of translocation breakpoints in seven uterine leiomyomata 10 to >100 kb upstream of HMGI-C by use of fluorescence in situ hybridization. These findings suggest a different pathobiologic mechanism in uterine leiomyomata from that in lipomas. HMGI-C is the first gene identified in chromosomal rearrangements in uterine leiomyomata and has important implications for an understanding of benign mesenchymal proliferation and differentiation.

Recently, molecular dissection of this chromosomal region has substantiated this hypothesis. To identify a gene at the breakpoint on chromosome 12 in uterine leiomyomata, a high-density physical map of the t(12;14) breakpoint region was constructed and identified a YAC, 981f11, that spans the translocation breakpoints in a uterine leiomyomata, pulmonary chondroid hamartoma and a lipoma. Further detailed characterization showed that the gene for HMGI-C, an architectural factor that is a non-histone component of chromatin, maps within 981f11 and is disrupted in lipomas. HMGI-C is rearranged in lipomas with chromosome 12 translocations, resulting in novel chimeric transcripts that fuse the DNA-binding A-T hook domains of HMGIC with potential transcriptional activation domains.

Applicants' invention, as recited in the amended claims, is directed to a method for treating obesity in a mammal by reducing the biological activity of HMGI genes in the mammal which comprises the steps of administering to a mammal a therapeutically effective amount of an inhibitor compound to inhibit the protein-protein interactions of HMGI proteins. Applicants' invention is also directed to a method for regulating growth and development of adipose tissue in a mammal by reducing the biological activity of HMGI genes in the mammal which comprises the steps of administering to a mammal a therapeutically effective amount of an inhibitor compound to inhibit the protein-protein interactions of HMGI proteins.

Accordingly, the Examiner's rejection of claims 6-12, 17-19, 23-25 and 30-32 are rejected under 35 U.S.C. 112, first paragraph, should be withdrawn.

It has been consistently held that the first paragraph of 35 U.S.C. Section 112 required nothing more than objective enablement.... In satisfying the enablement requirement, an application need not teach, and preferably omits, that

which is well-known in the art.... How such a teaching is set forth, whether by the use of illustrative examples or by broad descriptive terminology, is of no importance since a specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as complying with the first paragraph of 35 U.S.C. Section 112 unless there is reason to doubt the objective truth of the statements relied upon therein for enabling support... The error we see in Staehelin's approach to the question before us is that Staehelin would require a patent specification to be a blueprint which, if followed, would unfailingly reproduce exactly an applicant's claimed invention. However, the law does not require a specification to be a blueprint in order to satisfy the requirement for enablement under 35 USC Section 112, first paragraph. *Staehelin v. Secher*, 24 U.S.P.Q.2d 1513, 1516 (B.P.A.I 1992).

In order to be entitled to the benefit thereof, it is not necessary that a patent application exactly describe the limitations of a claimed process, but only so clearly that those skilled in the art would recognize from the disclosure that applicant invented the claimed process, including those limitations. *In re Wertheim et al.*, (C.C.P.A. 1976) 541 F2d 257, 191 U.S.P.Q. 90.

In view of the foregoing response, applicant requests reconsideration pursuant to 37 C.F.R. Section 112 and allowance of the claims pending in this application. Applicant requests the Examiner to telephone the undersigned attorney should the Examiner have any questions or comments which might be most expeditiously handled by a telephone conference.

Applicant's attorney authorizes the Examiner to charge Deposit Account 13-4822 if there are any additional fees due in connection with this response.

Respectfully submitted,
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